The effect of resin infiltration on proximal caries lesions in primary and permanent teeth. A systematic review and meta-analysis of clinical Trials

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Abstract: INTRODUCTION/OBJECTIVES This systematic review aimed to critically appraise the evidence on resin infiltration for the clinical management of proximal caries lesions in primary and permanent teeth. DATA Search terms included resin infiltration, micro-invasive and proximal caries. Potentially eligible studies involved proximal caries lesions treated with resin infiltration. Risk of bias assessment was performed using the Cochrane risk of bias tool and the quality of evidence was assessed with GRADE. SOURCES Electronic Database search of published and unpublished literature was performed in April 22, 2018 within the following databases: MEDLINE via Pubmed, Cochrane Central Register of Controlled Trials, LILACS via BIREME, Open Grey, Clinical Trials.gov and National Research Register. STUDY SELECTION Of 135 articles initially retrieved, 10 were eligible for inclusion in the systematic review comprising the results of 9 studies, while 5 randomized controlled trials (RCTs) (6 articles) with unclear risk of bias contributed to the meta-analyses. Random effects meta-analyses were implemented and lesion progression treatment effects were estimated through Odds Ratios (ORs) along with associated 95% Confidence Intervals (95% CIs). CONCLUSIONS Overall, there was strong evidence that proximal caries lesion progression was less likely to occur in permanent teeth following treatment with resin infiltration plus oral hygiene measures as compared to non- invasive methods (oral hygiene instructions) for follow up 18 months to 2 years (3 studies: OR = 0.14; 95% CI: 0.08, 0.25; $P < 0.001$) as well as 3 years (4 studies: OR = 0.15; 95% CI: 0.06, 0.36; $P < 0.001$). The quality of the evidence was rated as moderate to low respectively.

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Sources: Electronic Database search of published and unpublished literature was performed in April 22, 2018 within the following databases: MEDLINE via Pubmed, Cochrane Central Register of Controlled Trials, LILACS via BIREME, Open Grey, Clinical Trials.gov and National Research Register).

Study Selection: Of 135 articles initially retrieved, 10 were eligible for inclusion in the systematic review comprising the results of 9 studies, while 5 randomized controlled trials (RCTs) (6 articles) with unclear risk of bias contributed to the meta-analyses. Random effects meta-analyses were implemented and lesion progression treatment effects were estimated through Odds Ratios (ORs) along with associated 95% Confidence Intervals (95% CIs).

Conclusions: Overall, there was strong evidence that proximal caries lesion progression was less likely to occur in permanent teeth following treatment with resin infiltration plus oral hygiene measures as compared to non- invasive methods (oral hygiene instructions) for follow up 18 months to 2 years (3 studies: OR=0.14; 95%CI: 0.08, 0.25; P<0.001) as well as 3 years (4 studies: OR= 0.15; 95%CI: 0.06, 0.36; P<0.001). The quality of the evidence was rated as moderate to low respectively.

Clinical Significance

Halting the progress of interproximal non cavitated lesions confined up to 1/3 of the dentin, is of considerable importance for caries management. The synthesis of the available evidence provides useful insights to promote clinical decision making based on optimal clinical practices.

1. Introduction

While there has been a dramatic reduction in caries prevalence for occlusal surfaces, only a meager decline has taken place for proximal surfaces [1]. Proximal caries may comprise more than half of all reported caries [2]. In primary molars, the percentage of proximal caries lesions may be higher, varying from 30 to 75% [3, 4, 5]. The progression of interproximal caries from early decalcification to cavitation has been of great interest, for its clinical implications because if detected early before cavitation level, caries can be managed with preventive protocols or micro invasive interventions [6]. Cavitation is considered by most as the threshold to institute operative treatment, the higher the lesion's ICDAS category, the higher the chance for the proximal surface to be cavitated [7]. Furthermore, the progression of the lesion is related to the baseline ICDAS lesion severity [8], the more intact surfaces being more resistant to caries progression [9]. Therefore, intervention to preserve demineralized enamel in non cavitated lesions and halt any progression, , would be a rather beneficial caries management approach, both for primary and permanent teeth, in order to prevent subsequent restoration..

Customarily, interproximal lesions have been treated using ordinary invasive restorative (drill and fill) methods [10]. The restorative approach involves the removal of sound tooth structure along with the removal of the carious tissues [11]. The durability of restorations is limited and the initial invasive intervention often brings the tooth into a circle of treatment and re-treatment, known as the 'death spiral of restorations' [12]. Consequently, noninvasive measures have been developed with promising results on halting the lesion progression. These measures include oral hygiene intensified protocols by mechanical removal of plaque with flossing or interdental brushing, dietary advice, chemical control of cariogenic bacterial load by in office application of chlorhexidine varnishes, or re-mineralizing treatments with in office topical fluoride or home use of casein phosphopeptide [13,14,15]. However, the effectiveness of the above measures may be compromised by poor patient compliance and recall visits treatment costs [16-21].

Thus, micro-invasive approaches where introduced as alternative to preventive measures for the management of non cavitated proximal carious lesions, up to the outer third of dentin, being independent to patient compliance and more conservative than standard invasive restorative approaches. Such micro-invasive methods already used are polyurethane foils [22], low viscosity composite resins and dental adhesives [23-26] and sealants [27]. Their success rate however is not as promising since despite their potential to form a resin layer on the tooth surface, the penetration of porous decalcified enamel is superficial [28]. Hence, another concept, namely caries infiltration was introduced as a proximal micro-invasive treatment approach, aiming in infiltrating the porous body of the lesion as well as establishing a diffusion barrier within the tooth. Diffusion pathways for cariogenic acids and dissolved minerals are occluded, thus halting the demineralization process before it has reached cavitation [29]. The concept of caries infiltration was first developed at the Charité Berlin as a micro-invasive approach for the management of smooth surface and proximal non-cavitated caries lesion [30]. It is marketed under the name Icon (DMG America Company, Englewood, NJ). Caries infiltration utilizes capillary forces to carry methacrylic resins with high penetration coefficients (infiltrants) into the porous enamel. Enamel is etched using HCl 15% rather than phosphoric acid to remove the pseudo-intact surface layer [31].

Resin infiltration is a promising technique that could reduce the loss of dental hard tissue and avert costly treatments. Furthermore, resin infiltration depends less on patient's compliance thus providing increased efficacy. However there is still uncertainty about resin infiltration's success as compared to standard invasive and non-invasive preventive treatments. Previous systematic reviews [32,33], have shown promising results considering the use of resin infiltration technique for interproximal early caries, however, the need to assess the latest evidence provided by the most recent clinical trials as well as to conduct a quantitative synthesis of the current data, indicated the need for the present systematic review. Therefore, the objective of this review was to provide a comprehensive synthesis of resin infiltration effect in vivo, on early proximal caries lesions in the primary and permanent teeth.

2. Material and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [34,35] were followed for reporting of this systematic review.

2.1 Eligibility Criteria

The following inclusion/exclusion criteria were applied for this systematic review:

- Study design: Randomized Controlled Trials (RCTs) or Controlled Clinical Trials (CCTs) were considered. Both parallel and split-mouth designs were eligible.
- Participants: Patients (children and/or adults) in primary or mixed/permanent dentition with proximal caries lesions, extending at enamel to the outer third of dentin.
- Intervention: Resin Infiltration (with or without non-invasive methods such as dental floss, fluoride).
- Comparator: Other micro-invasive treatment technique or non-invasive methods (control) such as dental floss, fluoride.
- Outcome measures: Lesion progression after application of treatment (assessed with any type of radiographic or clinical measure).
- Exclusion Criteria: Studies involving patients with systematic or other diseases, patients undergoing orthodontic treatment, lesions other than proximal (ie. Labial/lingual surface lesions).

2.2 Search Strategy

Electronic search within the following databases was undertaken in September 30, 2017 and updated in April 22, 2018, while no language restrictions were applied: Medline via Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS via BIREME Virtual Health Library. Moreover, unpublished literature was searched in Open Grey, ClinicalTrials.gov (www.clinicaltrials.gov) and the National Research Register (www.controlled-trials.com), using the terms (resin infiltration) AND (proximal lesion). Hand searching of the reference lists of the retrieved full text articles was also conducted. Authors of original studies were contacted for data clarification if needed. Full search strategy employed in Medline via Pubmed is presented in Appendix 1.

Eligibility assessment, data extraction and Risk of Bias (RoB) assessment was implemented independently and in duplicate by two reviewers (SC and DK), while disagreements were resolved through discussion and after consultation with a third author (KK).

2.3 Data Extraction

Data extraction was performed by two independently working reviewers (SC and DK) on standardised piloted forms who were not blinded to author identity and study origin. Titles and abstracts were examined first, followed by full text screening of the potential for inclusion articles. Information was obtained from each eligible study on study design, methods, participants, interventions, comparators and outcomes, observation period and adverse effects.

2.4 Risk of bias within studies

Risk of bias in individual studies was assessed according to the Cochrane Risk of Bias tool [36]. In particular, the following domains were considered: 1. random sequence generation, 2. allocation concealment, 3. blinding of participants and/ or personnel involved in the study, 4. blinding of assessors, 5. incomplete outcome data reporting, 6. selective reporting of outcomes, 7. other sources of bias (including industry related bias or professional interest). An overall assessment of the risk of bias was made for each included study (high, unclear, and low). Trials with at least 1 item designated to be at high risk of bias were regarded as having an overall high risk of bias. Trials with unclear risk of bias for one or more key domains were considered to be at unclear risk of bias and trials with low risk of bias in all domains were rated as low risk of bias.

2.5 Summary Measures and Data Synthesis

Clinical heterogeneity of included studies was assessed through the examination of individual trial settings, eligibility criteria, treatment methods used and data collection methods. Statistical heterogeneity was examined through visual inspection of the confidence intervals (CIs) for the estimated treatment effects on forest plots. Also, a chi-square test was applied to assess heterogeneity; a p-value below the level of 10%

($p<0.1$) was considered indicative of significant heterogeneity [37]. I^2 test for homogeneity was also undertaken to quantify the extent of heterogeneity.

Only studies at unclear or low risk of bias overall were included in meta-analyses. Random effects meta-analyses were conducted as they were considered more appropriate to better approximate expected variations in trial settings. Treatment effects were calculated through Odds Ratios (ORs) for lesion progression along with associated 95% Confidence Intervals (95% CIs).

2.6 Risk of bias across studies

If more than 10 studies were included in meta-analysis, publication bias was to be explored through standard funnel plots [38].

2.7 Additional Analyses

Sensitivity analyses were pre-determined to explore and isolate the effect of studies with unclear risk of bias on the overall treatment effect if both low and unclear risk of bias studies were included.

All analyses were undertaken in Stata version 15.1 software (StataCorp, College Station, Texas, USA) using the command "metan".

2.8 Quality of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) were implemented to assess the overall quality of evidence as formulated by the interventions and the outcomes under evaluation [39,40]. According to GRADE the overall body of evidence is rated as high, moderate, low and very low. High quality of evidence means that further research is very unlikely to change our confidence in the estimated effect. Moderate: further research is likely to have an important impact on our confidence in the estimated effect and may change the estimate; low: further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate; very low: any estimated effect is very uncertain. Assessment is made in relation to the following domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. For the first 4 domains the quality of evidence may be downgraded on the

basis of either ‘serious’ or ‘very serious’ risks (3 levels); publication bias may either be suspected or undetected (2 levels).

3. Results

3.1 Search Details

The results of the study selection process are presented in Figure 1. One hundred and thirty five studies were initially identified after full database electronic search as well as hand searching. Following full text assessment, 9 studies were considered eligible for inclusion in the review, consisting of 10 articles [41-50] as one was a follow-up report [44]. Five studies were eligible for quantitative synthesis, again consisting of 6 articles.

3.2 Study design and Characteristics

All included studies were randomized controlled trials with split-mouth design (Table 1). They were published from 2010 onwards until 2018, one trial within the repository it has been registered [50] while two others as theses [45,46]. Four studies originated from Europe (3 from Germany [41,43,44], 1 from Denmark [47]), three from Brazil [45,46,49], one from the United States [50], one from Colombia [42] and one from India [48].

Four studies [45,47-49] were conducted in primary teeth in children, with mean age ranging from 5.8 to 11 years old. The lesions sample size tested by the included studies was between 32 and 84. The rest of the studies [41-44,46,50] were designed to assess lesions in the permanent dentition. The mean age of the participants in these studies ranged from 21.1 to 25 years, while the sample size examined was between 44 and 186 lesions.

All trials used resin infiltration as the intervention of primary interest which was applied to lesions extending up to 1/3 of the outer dentin layer and was typically administered in conjunction with other non-invasive instructions for oral hygiene, flossing and application of fluoride and/or fluoride supplements. Comparison

interventions mainly comprised of non-invasive, placebo control interventions including flossing, instructions for diet and fluoridation. In one study [42], sealing application methods were used as a comparator.

All but two studies[47,48] recorded lesion progression through pair-wise reading of conventional radiography, while some of those studies used digital subtraction radiography[42-44,50] as an additional means for outcome identification. Ekstrand et al, 2010 [47] and Rai et al, 2016 [48] described the use of visual caries assessment through ICDAS scoring system [51], supplemented by certain radiographic scores (ie area under histograms). The evaluation period for outcome assessment ranged from 3 months [45] to 3 years [42,44,46,50] (Table 1).

3.3 Risk of bias within studies

Overall, risk of bias was rated as unclear in six studies (7 articles) [41-44,46,49,50], and high in three [45,47,48]. Generation of random sequence for treatment allocation was adequately reported in all trials, while for allocation concealment this was the case for half of the studies [41,43,44,47,50]. Although blinding of participants was adequately described in all but one studies [45], blinding of personnel involved in the trial was not clear and this might potential bear an impact on the effectiveness of treatment provided (ie instructions for oral hygiene measures). Again, only one study [45] failed to report masking of the outcome assessor. For the majority of the studies, attrition bias was not suspected; however, 2 trials [46,50] reported a significant amount of dropouts during the course of the treatment. Risk of bias due to selective reporting was low in 5 studies [41,43-46,49]. Interestingly, two studies [47,48] failed to present the results of all pre-specified time-points, while in one study [50], it was not clear whether digital subtraction radiography was performed, although pre-specified. Ekstrand et al, 2010 [47] was rated high risk of bias for additional parameters, as although the study followed a randomization scheme, it presented unbalanced allocation of lesions according to ICDAS scoring system. Lastly, two studies (3 articles) [41,43,44] were suspected for industry related bias as the founders of the assigned intervention (ie, product used) were involved in authorship, while in one study [42], industry funding appeared to play a role on the presentation of the

results of the study and/ or publication. As such, these studies [41-44] were rated unclear with regard to other bias domain (Figure 2; Figure 3).

3.4 Effects of interventions, meta-analyses and additional analyses

The outcome of interest (ie lesion progression) was assessed in two time-spans: one included 18 months to 2 years assessment, and the other 3 years assessment. Both syntheses consisted of comparisons between resin infiltration plus oral hygiene measures (ie flossing, fluoridation etc), and merely non-invasive oral hygiene measures reported as control. Based on availability of information by the original studies, lesion progression assessed through pairwise conventional radiography is presented as pooled overall outcome and only studies pertaining to permanent teeth were eligible for data synthesis in the present review.

With regard to 18 months to 2 years follow up period, there was strong evidence that treatment with resin infiltration combined with non-invasive oral hygiene measures resulted in significantly lower odds for lesion progression as compared to pure non-invasive methods (control). In fact, resin infiltration had 86% lower odds for progression of lesions (3 studies: OR=0.14; 95%CI: 0.08, 0.25; P<0.001; Figure 4). No significant statistical heterogeneity was detected for this synthesis (I-squared= 0.0%; chi-squared: P= 0.77).

Considering 3 years follow-up, again there was strong evidence to support that lesion progression was less likely to occur after treatment with resin infiltration (4 studies: OR= 0.15; 95%CI: 0.06, 0.36; P<0.001). There was no evidence of statistically significant heterogeneity for this comparison as well (I-squared= 16.6%; chi-squared: P=0.31; Figure 5).

The four studies [45,47-49] performed in primary teeth were heterogeneous with regard to study settings or evaluation periods or suffered from inherent high risk of bias and could not be mathematically combined. Overall, Ekstrand et al, 2010 [47], assessed proximal lesions 1 year after the use of resin infiltration combined with fluoride varnish (test group) compared to fluoride varnish application (control group) and reported significantly higher ICDAS scores for the test group; however these visual assessment findings were

not confirmed by radiographic evaluation. Sarti 2015 [45], evaluated the same outcome after 3 months and compared resin infiltration supplemented by oral hygiene methods and pure oral hygiene methods. No difference was detected between the groups after assessment of pairwise radiographs. Another study [48], did not report any differences between lesions treated with or without chlorhexidine varnish supplementation after visual assessment of caries; however, radiographic evaluation using histogram parameters, revealed limited net increase in the area of carious lesion after 9 months in the group with varnish supplementation. Last, a recent study [49] reported that primary molars treated with resin infiltration combined with fluoride toothpaste and flossing presented lesion progression in only 12% of the cases whereas the figure was significantly larger for the control group (33%).

As only trials with unclear risk of bias were included in the syntheses, no additional sensitivity analyses were undertaken, although pre-specified.

3.5 Risk of bias across studies

Publication bias could not be explored either graphically or statistically as no more than 4 studies were combined within the syntheses overall.

3.6 Quality of the evidence

The assessment of the quality of evidence on proximal lesion progression in permanent teeth (lesions extending up to outer one third of dentin), revealed that the level of the existing evidence was moderate for the short term evaluation period (ie 18 months to 2 years). The findings suggest that further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate. The level of existing evidence was low for the long term follow up period (ie 3 years), showing that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate (Table 2).

4. Discussion

4.1 Summary of evidence

According to the results of the present systematic review, the management of proximal non- cavitated caries lesions, up to the outer third of dentin, with resin infiltration in conjunction with non-invasive oral hygiene/ preventive instructions is suggested to be a promising therapeutic approach for permanent teeth. Findings of post treatment follow up, for up to 3 years, supported that the progression of the lesions were halted in most cases and that treatment effects were improved when compared to non- active interventions. Furthermore for the primary teeth, no robust conclusions could be drawn for the effect of resin infiltration, mainly due to the scarcity of the available studies, the inherent risk of bias and the apparent heterogeneity in trial settings and means/ time-points of outcome evaluation.

Resin infiltrants were developed based on the rationale of deeper penetration and infiltration within the body of the lesion [6,52] as compared to regular adhesives[53,54]. As such, they are characterized by rapid capillary penetration, and display very low viscosity, low contact angle to the enamel and increased surface tension [55]. The clinical procedure followed for resin infiltration is considered rather simple and acceptable by the operators and patients [56]. Alternatively, for the management of non cavitated interproximal lesions, a promising technique maybe interproximal sealing with sealing materials or bonding adhesives after tooth separation with orthodontic elastic bands, requiring however two visits, while the evidence is limited. Nevertheless, when caries infiltration method is used there is no need for temporary tooth separation [57], which apparently simplifies the clinical application in a single appointment [58,59]. Furthermore, inhibition of the lesion is being achieved despite the fact that there is emerging debate with regard to the presence of bacteria at the bottom of proximal lesions that could potentially trigger the mechanism for caries development. It has been shown that the count of bacteria in non-cavitated lesions is low and not detrimental if properly sealed [53]. However, the promising technique of resin infiltration is not free of limitations; administration of local anesthesia maybe needed due to placement of a wedge in order to open the contact area and separate the interproximal tooth surfaces. The surface layer after resin infiltration is less homogenous than the surface layer after adhesives [55] and undetected micro-cavities on the surface of

the proximal infiltrated carious lesions may lead to additional plaque accumulation [60]. Micro-leakage can also occur due to polymerization shrinkage and polymerization stress of the infiltrant [61]. Thus, remaining surface roughness on infiltrated lesions attracting biofilm formation, may lead to possible further lesion demineralization and increase in roughness overtime, compromising the long term longevity of infiltrated lesions [62]. Although the findings of the present review were informative with regard to the potential effectiveness of resin infiltration treatment compared to non- invasive therapeutic approaches in permanent teeth, the necessity for further studies involving direct comparisons of more than one invasive treatment modalities and micro- invasive interventions seems imperative. The comparative effectiveness of resin infiltrants and dental adhesives, sealants or other minimally invasive methods for proximal sealing is yet to be investigated. Furthermore their long term longevity remains unclear.

In view of the most prevalent means for outcome assessment used by the included studies, all but two studies [47,48] recorded lesion progression through pair-wise reading of conventional radiography while four of them [42-44,50] used digital subtraction radiography as supplementary means for evaluation. Although most trials [41,43,44,46,48,49] involved more than one independent examiner when assessing the outcome (ie. reading of radiographs for identification of lesion progression), only three [43,44,49] were clear about initial training and calibration procedures between multiple examiners. The power of calibration procedures has well been recognized in dental research and especially in caries detection [63,64], while it becomes vital when subjectivity is involved in outcome evaluation. Higher levels of inter- examiner agreement would apparently contribute to overall increased precision when it comes to the detection of lesion progression.

All studies included in the meta-analyses were randomized controlled trials and could have potentially contributed to the highest level of evidence through their findings. However, the level of evidence for the outcome lesion progression for proximal lesions in permanent teeth was downgraded for both periods of evaluation (ie 18 months to 2 years and 3 years). For the time period involving 18 months to 2 years follow-up, the level of evidence was downgraded one level due to imprecision as all available studies involved

correlated data not accounted for (ie. multiple teeth nested within the same quadrant). For 3 years follow-up, the level of evidence was downgraded twice as apart from the likelihood for imprecision on the estimated outcome, risk of bias was also suspected. Specifically, the high level of dropouts contributed to the rating of unclear risk for attrition bias.

4.2 Strengths and Limitations

To our knowledge, this is the first systematic review that includes a thorough and quantitative synthesis on the effectiveness of resin infiltration for proximal caries management. This can be considered a potential strength of the present article, while it additionally follows a robust and detailed methodology and reporting scheme and includes an assessment of the quality and level of evidence overall for permanent teeth. In addition, a comprehensive literature search was employed in six databases including unpublished research data which in fact contributed to the available evidence. Previously conducted systematic reviews were either confined to qualitative synthesis of the available data with regard to resin infiltration of early proximal caries lesions [32,33], or did not follow a sound and systematic methodology for the identification and assessment of relevant articles and extraction of reproducible conclusions [32]. In addition, both reviews [32,33] included articles published until 2014, which constitutes a clear need for an update on the topic. However, the following limitations cannot be precluded. First, the review could not draw definite conclusions with regard to the effectiveness of resin infiltration for primary teeth due to the scarcity of the available trials designed in populations involving young children as well as the compromised internal validity of some. Second, the results of this review are confined to the effectiveness and applicability of resin infiltration as compared to standard oral hygiene measures; this was the case as no syntheses of the findings of individual studies involving other means of micro- invasive interventions could be conducted, in view of the lack of direct comparisons of resin infiltration technique with other methods. Third, with regard to study identification and data extraction methodology followed in this study, the reviewers involved in the screening process were not blinded to either author's names and/ or study origin. This might be considered a potential drawback; however, the reviewers worked independently, and consultation with a third reviewer was also

obtained for disentanglement of any disagreement. In fact, the Cochrane Collaboration for Systematic Reviews of Interventions emphasizes on data screening and extraction by at least two reviewers; blinding of the reviewers may be time consuming, while it does not warrantee benefit and protection against bias [65]. Furthermore, none of the reviewers/ authors of the present study has any potential interest to declare with regard to resin infiltration interventions used by any of the eligible articles for inclusion. Fourth, the confidence intervals/ limits of the pooled estimates in both meta- analyses employed should be interpreted with caution as they are based on correlated data not accounted for. The unit of analysis were teeth treated as independent data; normally, the confidence bounds would be further away from each other than they were recorded, apparently denoting decreased precision of the estimated effect. Currently, there is no widely applicable method of mathematical synthesis of individual studies involving correction of the effects of within cluster reduced variability (ie. increased dependence of teeth pairs within the same patients), when binary outcomes are involved. This is actually confirmed by the most recent Cochrane systematic review on the topic [33], although new approaches of mathematical simulation methods have been described for split-body interventions [66]. The present review was also prone to industry related bias as in two of the included trials (3 articles) [41,43,44], authors appeared to be actively involved (founders) with one of the products used for resin infiltration; however, it was not possible to estimate whether sponsorship and professional interest on their part was related to the trials' findings and presentation of their published results. To overcome such issues, non-industrial or state funding, coupled with external investigators and data analysists with data monitoring committees would be advisable in future research. Lastly, the likelihood of publication bias could not be detected although pre-specified as less than 10 studies were included; nevertheless, its presence cannot be precluded.

5. Conclusions

The use of resin infiltration for sealing of early interproximal lesions when combined with oral hygiene measures was promising and more effective than oral hygiene measures alone for follow- up periods of up to 3 years in permanent teeth (low to moderate quality evidence). However, no solid conclusions can be drawn

with regard to primary teeth. Overall, additional future trials should be designed at the highest standards of conduct and reporting to test the comparative effectiveness of resin infiltrants and other means of active interventions. This will smooth out uncertainty regarding treatment effects and will promote clinical decision making based on optimal clinical practices.

Protocol Registration

No

Funding

None

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Legends for Illustrations

Figure 1. PRISMA flow diagram of study selection

Figure 2. Risk of bias summary outlining judgement of risk of bias items for each included study. Green circles denote “low” risk of bias, yellow denote “unclear” and red “high” risk of bias

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 4. Random effects meta-analysis of lesion progression for resin infiltration and control (non-invasive) interventions at 18 months to 2 years

Figure 5. Random effects meta-analysis of lesion progression for resin infiltration and control (non-invasive) interventions at 3 years

Table 1. Characteristics of Included randomized controlled trials

Study	Participants	Intervention	Comparisons	Outcomes	Adverse Effects	Results of original studies with regard to Lesion Progression
Meyer-Lueckel 2016, split-mouth RCT	70 patients (41 female, 29 male), mean age 23±6years, 186 lesion pairs (permanent teeth)	Infiltration (ICON) plus instructions for a noncariogenic diet, flossing and fluoridation	Mock treatment (control) plus instructions for a noncariogenic diet, flossing and fluoridation	Lesion progression in pairwise reading of radiographs at 10 (only for high risk patients) and 18 months	none reported	At **18 months:** 10 in 186 for ICON and 58 in 186 for control
Martignon 2012, split-mouth RCT	39 patients (28 female, 11 male), mean age 21 years (range: 16-31), 117 lesions (3 each) (permanent teeth)	Infiltration (ICON-pre-product; DMG) plus instructions for flossing	test-B (Sealing: Prime-Bond-NT; Dentsply)/ Control-C placebo plus instructions for flossing on both groups	Lesion progression in pairwise reading of radiographs at 1, 2, 3 years and also Digital Subtraction Radiography (DSR) in year 1	none reported	**1 year**: 6 in 38 for ICON/ 11 in 38 for test-B and 18 for 38 in control-C. **2 years:** 9 in 37 for ICON/ 15 in 37 for test-B and 23 in 37 for control-C. **3 years**: 12 in 37 for ICON/ 15 in 37 for test-B and 26 in 37 for Control-C
Paris 2010, split-mouth RCT	22 patients (22 female, 8 male), mean age 25 years (range: 20-34), 58 lesions (permanent teeth)	Infiltration (ICON-pre-product; DMG) plus instructions for diet, flossing, and fluoridation	Placebo Control plus instructions for diet, flossing, and fluoridation	Lesion progression in pairwise reading of radiographs and DSR at 18 months	none reported	**conventional radiography at 18 months**: 1 in 27 for ICON/ 6 in 27 for control. **DSR at 18 months:** 2 in 27 and 10 in 27 respectively

Meyer-Lueckel 2012, split-mouth RCT (follow up of Paris 2010)	23 patients (22 female, 8 male), mean age 25 years (range: 20-34), 58 lesions (permanent teeth)	Infiltration (ICON-pre-product; DMG) plus instructions for diet, flossing, and fluoridation	Placebo Control plus instructions for diet, flossing, and fluoridation	Lesion progression in pairwise reading of radiographs and DSR at 3 years	none reported	**conventional radiography at 3 years**: 1 in 26 for ICON/ 9 in 26 for control. **DSR at 3 years:** 1 in 26 and 11 in 26 respectively
Sarti 2015, split mouth RCT	16 patients (9 female, 7 male), mean age 5.8±1.2 years, 32 lesions (primary teeth)	ICON and toothbrushing with fluoridated toothpaste and flossing instructions plus dietary recommendations plus sessions of professional fluoride application	Control and toothbrushing with fluoridated toothpaste and flossing instructions plus dietary recommendations plus sessions of professional fluoride application	Lesion progression in pairwise reading of radiographs and digital radiographs at 3 months	none reported	**At 3 months**: 2 in 16 for ICON/ 2 in 16 for control.
Pereira 2015, split mouth RCT	22 patients (13 female, 9 male), age range: 16-41, 72 lesions (permanent teeth)	ICON and toothbrushing with fluoridated toothpaste and flossing instructions plus dietary orientation and topical application of fluoride	Placebo Control and toothbrushing with fluoridated toothpaste and flossing instructions plus dietary orientation and topical application of fluoride	Lesion progression in pairwise reading of radiographs and digital radiographs at 3 years	none reported	**At 3 years**: 2 in 27 for ICON/ 5 in 27 for control

Ekstrand 2010, split mouth RCT	42 patients (23 female, 25 male), mean age 7.2 ±0.6 years, 84 lesions (primary teeth)	resin infiltration followed by fluoride varnish FV (2.26% F) application (test group)	Control only FV	Visual caries assessment using ICDAS scoring system AND radiographic scores (in 78 lesions)	none reported	**At 1 year:** the test group had significantly higher ICDAS scores than control; however this was not confirmed by the radiographic assessment
Rai 2016, split mouth RCT	38 patients (no sex reported), mean age 11 years, 76 lesions (primary teeth)	resin infiltration and an additional overlying layer of chlorhexidine varnish (test group)	resin infiltration only (control)	Visual caries assessment using ICDAS scoring system AND radiographic scores using histogram parameters for analysis	none reported	**At 9 months: ICDAS** revealed no statistically significant change in the area of the enclosed lesion (303±247 versus 213±115, P=0.246). **Radiographic evaluation** revealed that the net mean increase in area of the carious lesion was significantly lower in the test group versus control group (482±382 versus 234±101, P=0.006)
Ammari 2018, split mouth RCT	42 patients (23 female, 19 male), mean age 6.7±1.3, 84 lesions, (primary teeth)	resin infiltration plus fluoride toothpaste plus flossing	Control, only fluoride toothpaste and flossing	Lession progression in pairwise reading of radiographs at 1 year	none reported	**At 1 year:** 5 in 42 for ICON/ 14 in 42 for control
Peters NCT01496456, split mouth RCT	16 patients (12 female, 4 male), mean age 21.1±7.1, 44 lesions (permanent teeth)	Infiltration (ICON) plus dietary and behavioral modification, and fluoride supplements	Control, only dietary and behavioral modification, and fluoride supplements	Lesion progression in pairwise reading of radiographs and DSR at 3 years	none reported	**At 3 years:** 2 in 13 for ICON/ 11 in 13 for control

Table 2. Summary of Findings Table according to GRADE. Number of Lesions, effect estimates and quality of the evidence for Lesion Progression at 18 months to 2 years and at 3 years follow up

Resin Infiltration compared to Control for proximal caries lesions

Patient or population: patients with proximal caries lesions
Settings:
Intervention: Resin Infiltration
Comparison: Control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Lesions (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Resin Infiltration**				
Proximal Lesion Progression (18 months to 2 years)	**348 per 1000**	**70 per 1000** (41 to 118)	**OR 0.14** (0.08 to 0.25)	500 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
Proximal Lesion Progression (3 years)	**495 per 1000**	**128 per 1000** (56 to 261)	**OR 0.15** (0.06 to 0.36)	206 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Nested observations within participants (correlated) not taken into account
[2] Unclear risk for attrition bias due to high level of dropouts

Figure 1.

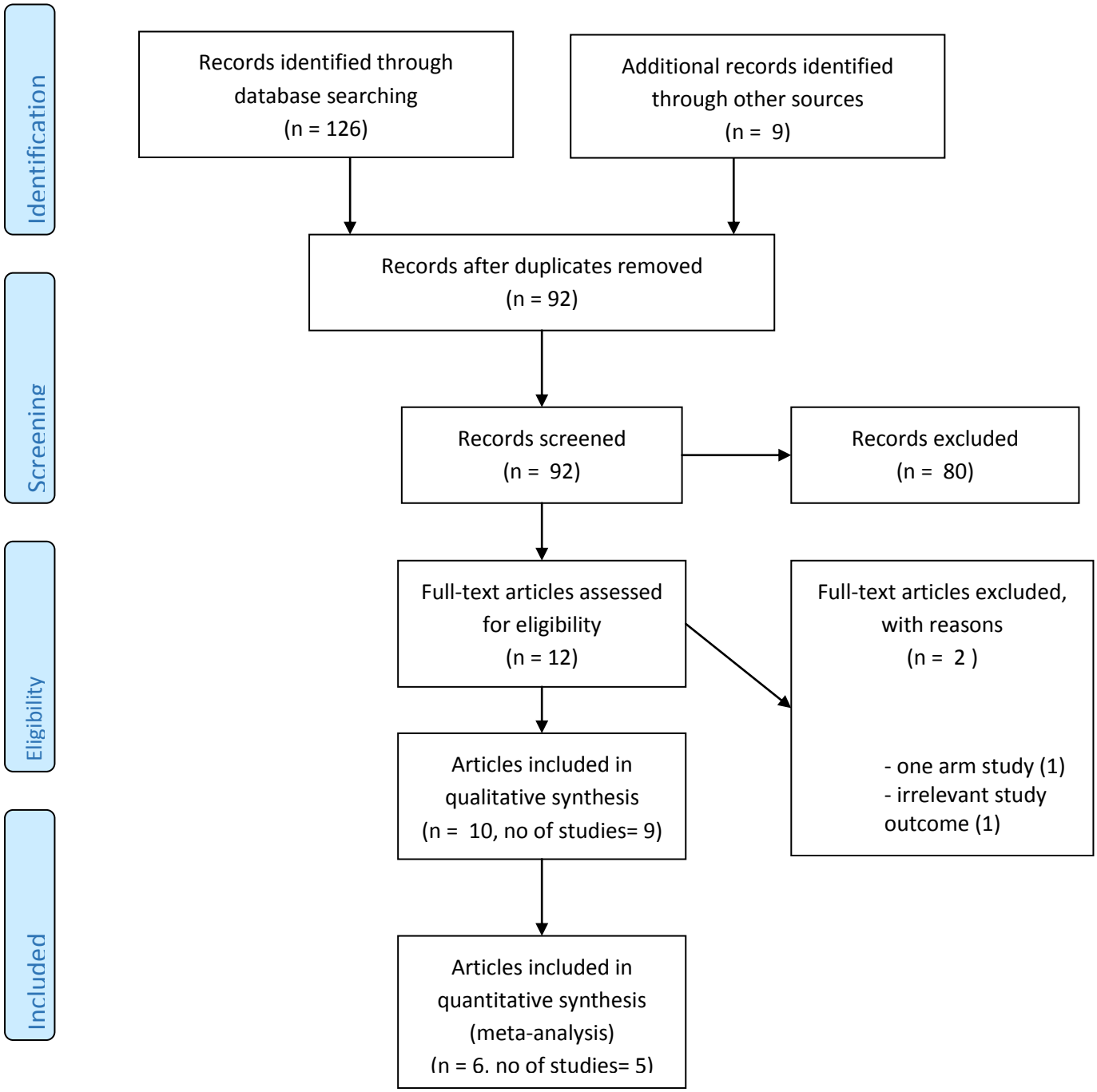

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 126)
Additional records identified through other sources (n = 9)
Records after duplicates removed (n = 92)
Records screened (n = 92)
Records excluded (n = 80)
Full-text articles assessed for eligibility (n = 12)
Full-text articles excluded, with reasons (n = 2)
- one arm study (1)
- irrelevant study outcome (1)
Articles included in qualitative synthesis (n = 10, no of studies= 9)
Articles included in quantitative synthesis (meta-analysis) (n = 6. no of studies= 5)

Figure 2

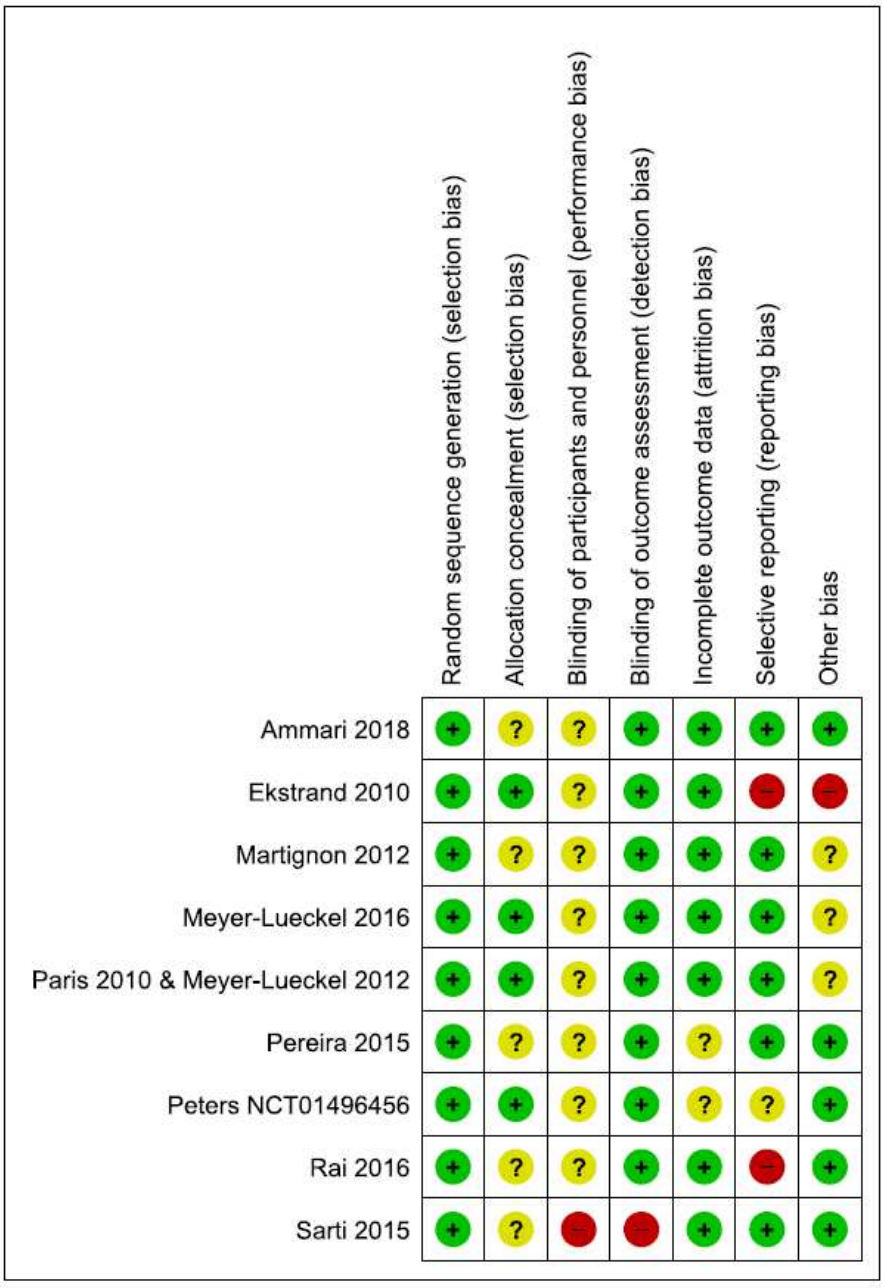

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Ammari 2018
Ekstrand 2010
Martignon 2012
Meyer-Lueckel 2016
Paris 2010 & Meyer-Lueckel 2012
Pereira 2015
Peters NCT01496456
Rai 2016
Sarti 2015

Figure 3

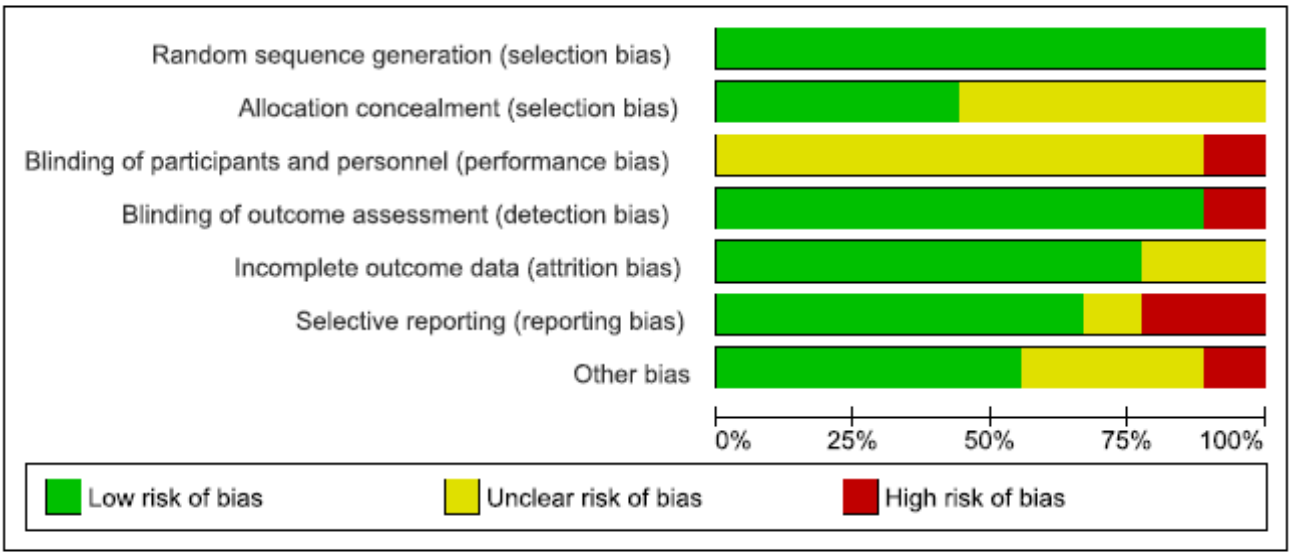

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 4

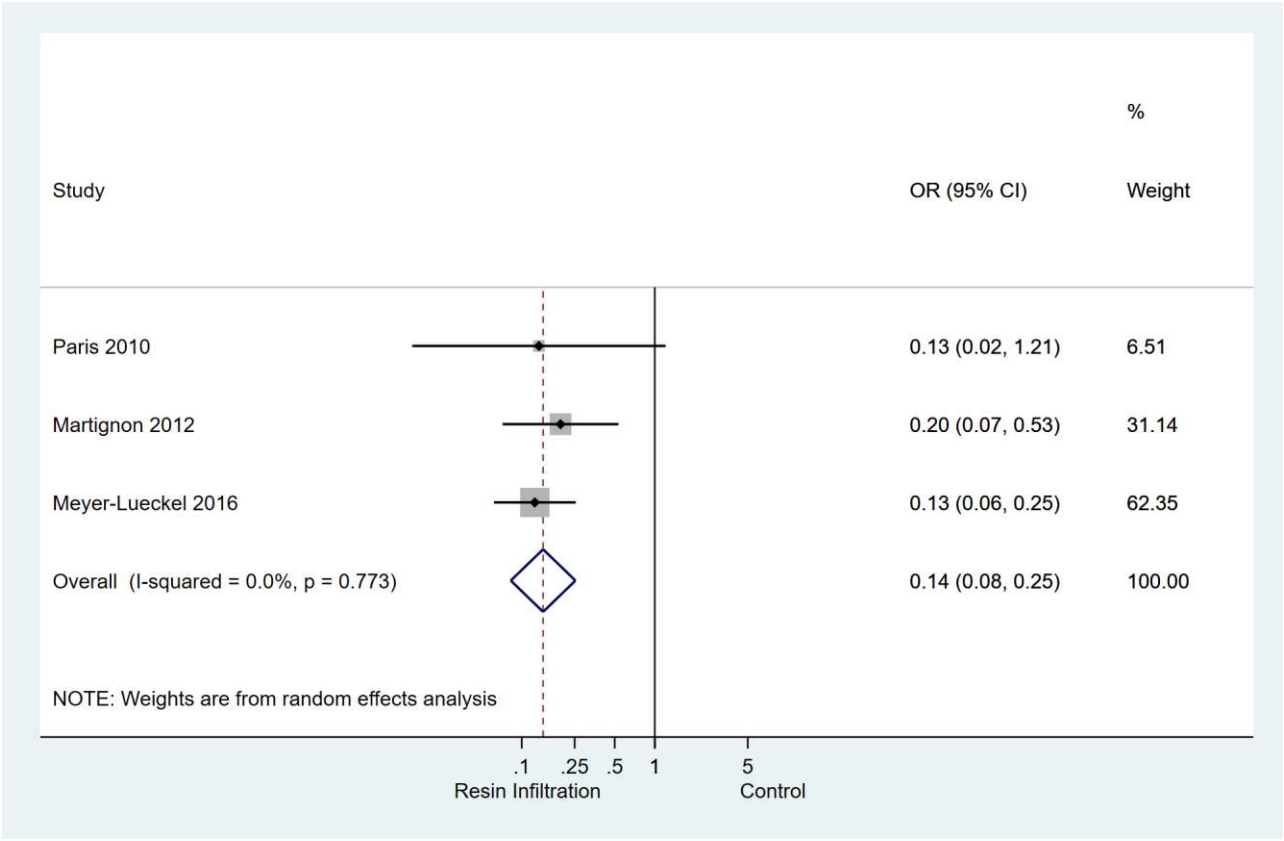
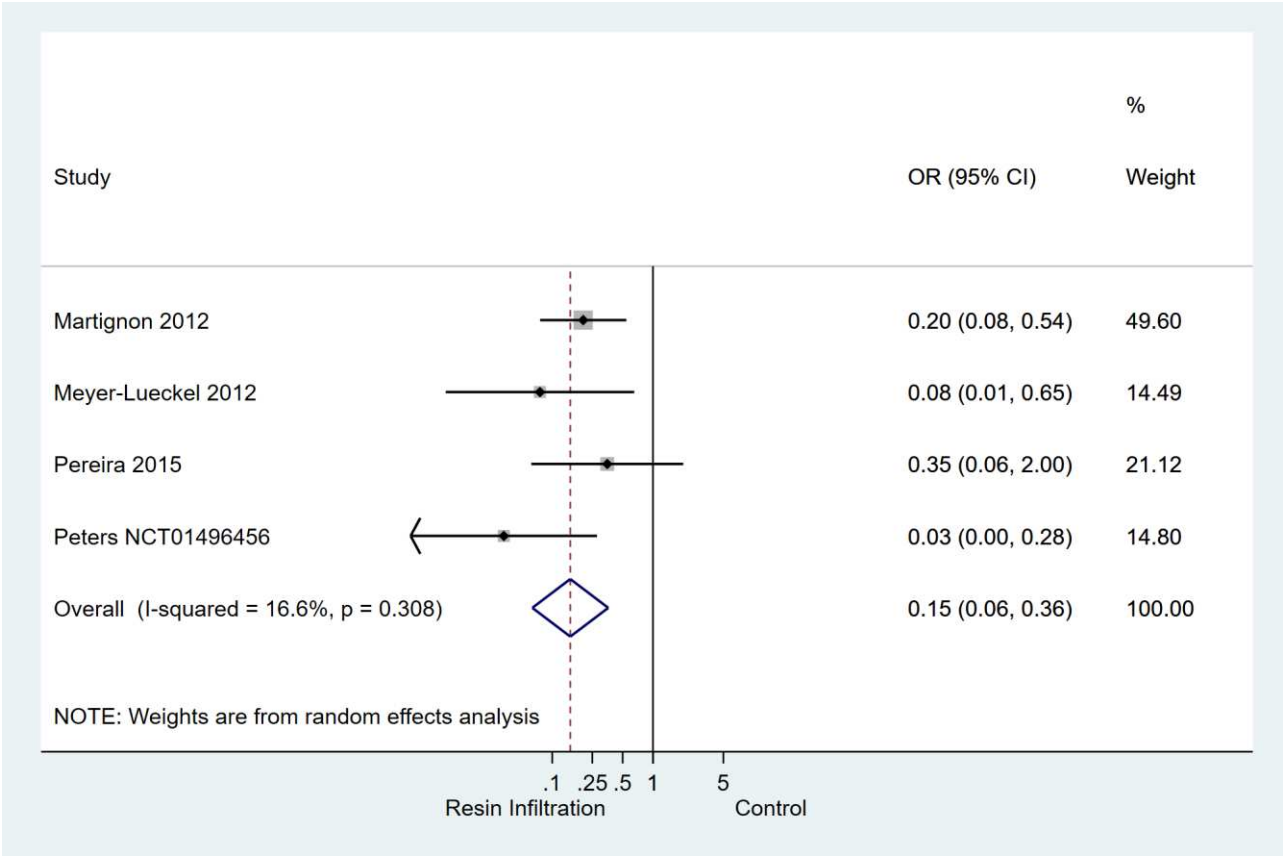

Study
OR (95% CI)
%
Weight
Paris 2010
0.13 (0.02, 1.21)
6.51
Martignon 2012
0.20 (0.07, 0.53)
31.14
Meyer-Lueckel 2016
0.13 (0.06, 0.25)
62.35
Overall (I-squared = 0.0%, p = 0.773)
0.14 (0.08, 0.25)
100.00
NOTE: Weights are from random effects analysis
.1
.25
.5
1
5
Resin Infiltration
Control

Figure 5


Study
OR (95% CI)
%
Weight
Martignon 2012
0.20 (0.08, 0.54)
49.60
Meyer-Lueckel 2012
0.08 (0.01, 0.65)
14.49
Pereira 2015
0.35 (0.06, 2.00)
21.12
Peters NCT01496456
0.03 (0.00, 0.28)
14.80
Overall (I-squared = 16.6%, p = 0.308)
0.15 (0.06, 0.36)
100.00
NOTE: Weights are from random effects analysis
.1
.25
.5
1
5
Resin Infiltration
Control

Appendix 1

MEDLINE search

Limits: no language restriction applied

Publication date: no restriction

Search Builder: 'All Fields'

Three consecutive searches combined with "AND" Boolean operator, using "OR" between free text terms or keywords:

1. ICON
2. resin infiltration
3. resin infiltra*
4. composite infiltration
5. composite infiltra*
6. micro-invasive
7. microinvasive
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. lesion progression
10. caries progression
11. lesion progress*
12. caries progress*
13. lesion development
14. caries development
15. white spot
16. white spot lesion
17. caries change
18. lesion change
19. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. proximal
21. proximal surface
22. proxim* surface
23. proxim*
24. primary dentition
25. permanent dentition
26. primary molar
27. primary teeth
28. permanent molar
29. premolar
30. deciduous teeth
31. deciduous molar
32. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31
33. 8 AND 19 AND 32